



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 0 846 689 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
10.06.1998 Bulletin 1998/24

(21) Application number: 97309761.1

(22) Date of filing: 03.12.1997

(51) Int Cl.⁶: C07D 235/08, C07D 235/10,
C07D 235/12, C07D 235/14,
C07D 235/16, C07D 401/06,
C07D 413/06, A61K 31/415,
A61K 31/42, A61K 31/44

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 09.12.1996 WOPCT/IB96/01395

(71) Applicant: PFIZER INC.
New York, N.Y. 10017 (US)

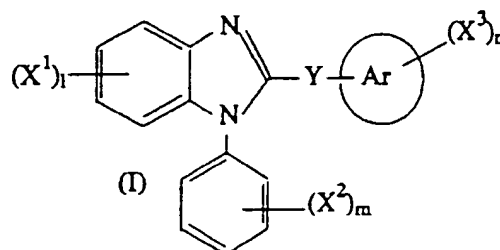
(72) Inventors:
• Mano, Takashi
Handa-shi, Aichi-ken 475 (JP)

• Okumura, Yoshiyuki
Chita-shi, Aichi-ken 478 (JP)
• Stevens, Rodney W.
Handa-shi, Aichi-ken 475 (JP)

(74) Representative: Ruddock, Keith Stephen et al
Pfizer Limited,
European Patent Department,
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

(54) Benzimidazole compounds

(57) This invention provides a compound of the following formula:



and the pharmaceutically acceptable salts thereof wherein

Ar is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl; X² and X³ are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfanyl, C₁₋₄ alkylsulfonyl or the like; X¹ is H, halo, C₁₋₄ alkyl, hydroxy, cyano, nitro, C₁₋₄ alkylthio, C₁₋₄ alkylsulfanyl, C₁₋₄ alkylsulfonyl or the like; Y is -CR¹=CR²- or -C≡C-, wherein R¹ and R² are independently H, methyl, ethyl or halo; and 1 is 0, 1, 2, 3 or 4; m and n are independently 0, 1, 2 or 3, with the proviso that when Ar is phenyl; and 1, m and n are 0, Y is not -CH=CH-; and when Ar is phenyl; l and m are 0; n is 1; and Y is -CH=CH-, X³ is not C₁₋₄ alkoxy attached to the 2-position of Ar, nor amino, C₁₋₄ alkylamino or di(C₁₋₄)alkylamino attached at 4-position of Ar; and a pharmaceutical composition useful for the treatment of a medical condition in which prostaglandins are implicated as pathogens.

EP 0 846 689 A1

Atty. Docket No. 6794S-5/US/USC
Serial No. 10/031,898
Kararli, et al.
Reference 67 of 69

Description**Technical Field**

This invention relates to novel benzimidazole cyclooxygenase inhibitors. The compounds of this invention inhibit the biosynthesis of prostaglandins by intervention of the action of the enzyme cyclooxygenase on arachidonic acid, and are therefore useful in the treatment or alleviation of inflammation and other inflammation associated disorders in mammals. This invention also relates to pharmaceutical compositions comprising such compounds.

Background Art

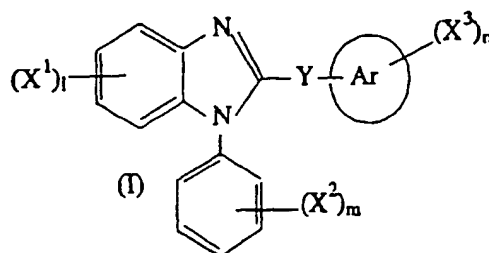
Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used in treating pain and the signs and symptoms of arthritis because of their analgesic and antiinflammatory activity. It is accepted that common NSAIDs work by blocking the activity of cyclooxygenase (COX), also known as prostaglandin G/H synthase (PGHS), the enzyme that converts arachidonic acid into prostanooids. Prostaglandins, especially prostaglandin E₂ (PGE₂), which is the predominant eicosanoid detected in inflammation conditions, are mediators of pain, fever and other symptoms associated with inflammation. Inhibition of the biosynthesis of prostaglandins has been a therapeutic target of antiinflammatory drug discovery. However, use of conventional NSAIDs is limited due to adverse side effects, notably gastrointestinal and renal toxicities.

Recently, two forms of COX were identified, a constitutive isoform (COX-1) and an inducible isoform (COX-2), of which expression is upregulated at sites of inflammation (Vane, J. R.; Mitchell, J. A.; Appleton, I.; Tomlinson, A.; Bishop-Bailey, D.; Croxtoll, J.; Willoughby, D. A. *Proc. Natl. Acad. Sci. USA*, 1994, 91, 2046). COX-1 is thought to play a physiological role and to be responsible for gastrointestinal and renal protection. On the other hand, COX-2 appears to play a pathological role and to be the predominant isoform present in inflammation conditions. A pathological role for prostaglandins has been implicated in a number of human disease states including rheumatoid and osteoarthritis, pyrexia, asthma, bone resorption, cardiovascular diseases, nephrotoxicity, atherosclerosis, hypotension, shock, pain, cancer, and Alzheimer disease. The NSAIDs currently on market inhibit both isoforms of COX with little variation for selectivity, explaining their beneficial (inhibition of COX-2) and deleterious effects (inhibition of COX-1). It is possible that a selective inhibitor of COX-2 may eliminate the side effects associated with COX-1 inhibition while providing antiinflammatory effects.

A variety of benzimidazole compounds are known and are disclosed in several patent applications. Specifically, Japanese Kokai (laid-open) Publication Number S49-81369 discloses 1-benzyl-benzimidazole compounds as antiinflammatory agents. Japanese Kokai (laid-open) Publication Number S59-75257 and H06-194780 disclose a variety of benzimidazole compounds as electrophotographic materials.

Brief Disclosure of the Invention

The present invention provides a compound of the following formula:



and the pharmaceutically acceptable salts thereof wherein:

Ar is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl which is connected to Y through a carbon atom, the heteroaryl being selected from pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isooxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl and tetrazolyl;

X¹ is H, halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkyl (preferably C₁₋₄ alkyl substituted by 1 to 5 halogen atom), hydroxy-substituted C₁₋₄ alkyl, (C₁₋₄)alkoxy(C₁₋₄)alkyl, amino, C₁₋₄ alkylamino, di(C₁₋₄)alkylamino, amino C₁₋₄ alkyl, (C₁₋₄)alkylamino(C₁₋₄)alkyl, di(C₁₋₄)alkylamino(C₁₋₄)alkyl, C₁₋₄ alkanoylamino, di(C₁₋₄)al-

kanoylamino, (C₁₋₄)alkyl(C₁₋₄ alkanoyl)amino, C₁₋₄ alkylsulfonylamino, C₁₋₄ alkanoyl, carboxyl, (C₁₋₄)alkoxycarbonyl, aminocarbonyl, (C₁₋₄)alkylaminocarbonyl, di(C₁₋₄)alkylaminocarbonyl, cyano, nitro, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylaminosulfonyl or di(C₁₋₄) alkylaminosulfonyl;

X² and X³ are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkanoyl, carboxyl, (C₁₋₄)alkoxycarbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl, di(C₁₋₄)alkylaminocarbonyl, cyano, nitro, amino, C₁₋₄ alkylamino, di(C₁₋₄)alkylamino or C₁₋₄ alkylsulfonylamino;

Y is -CR¹=CR²- or -C≡C-, wherein R¹ and R² are independently H, methyl, ethyl or halo;

1 is 0, 1, 2, 3 or 4 (preferably 0, 1 or 2); and

m and n are independently 0, 1, 2 or 3 (preferably 0, or 2),

with the proviso that when Ar is phenyl; and 1, m and n are 0, Y is not -CH=CH-; and when Ar is phenyl; 1 and m are 0; n is 1; and Y is -CH=CH-, X³ is not C₁₋₄ alkoxy attached to the 2- position of Ar, nor amino, C₁₋₄ alkylamino or di(C₁₋₄)alkylamino attached at the 4-position of Ar.

The benzimidazole compounds of the present invention exhibit inhibition of COX activity. Preferably compounds of this invention exhibit inhibitory activity against COX-2, with more preferable compounds having COX-2 selectivity.

Accordingly, the present invention also provides a pharmaceutical composition, useful for the treatment of a medical condition in which prostaglandins are implicated as pathogens, which comprises a compound of the formula (I): wherein Ar, Y, X¹, X², X³, 1, m and n are as defined above, and the pharmaceutically acceptable salts thereof.

Further, the present invention provides a method for the treatment of a medical condition in which prostaglandins are implicated as pathogens, in a mammalian subject, which comprises administering to said subject a therapeutically effective amount of said pharmaceutical composition.

The medical conditions in which prostaglandins are implicated as pathogens, include the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis including rheumatoid arthritis, degenerative joint disease (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures.

The compounds and pharmaceutical composition of this invention may inhibit cellular neoplastic transformations and metastatic tumor growth and thus may be used in the treatment of cancer. The compounds and pharmaceutical composition of this invention were used in the treatment and/or prevention of cyclooxygenase-mediated proliferation disorders such as which occur in diabetic retinopathy and tumor angiogenesis.

The compounds and pharmaceutical composition of this invention may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders, use in the treatment of Alzheimer's disease, and for the treatment of bone loss (treatment of osteoarthritis) by their ability to inhibit prostanoind-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids.

Furthermore, such compounds and pharmaceutical compositions which show specificity for COX-2 over COX-1, will prove useful as an alternative to conventional NSAIDs particularly where such NSAIDs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a redurated history of GI lesions, GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; prior to surgery of taking of anticoagulants.

Detailed Disclosure of the Invention

As used herein, "halo" is fluoro, chloro, bromo or iodo.

Preferred compounds of this invention are those of the formula (I) wherein Ar is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl selected from pyridyl, pyrrolyl and oxazolyl; X² and X³ are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; X¹ is H, halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkyl, amino, C₁₋₄ alkylamino, cyano or nitro; 1 is 0 or 1; and m and n are independently 0 or 1.

More preferred compounds of this invention are those of the formula (I) wherein Ar is phenyl or C₃₋₈ cycloalkyl; X² and X³ are independently, halo, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; X¹ is H, halo, amino, cyano or nitro, which is attached to 5- or 6-ring position of the benzimidazole ring system; and Y is -CR¹=CR²-, wherein R¹ and R² are independently H or methyl.

Further preferred compounds of this invention are those of the formula (I) wherein Ar is phenyl, cyclopentyl or cyclohexyl; X² and X³ are independently, fluoro, methylthio, methylsulfinyl or methylsulfonyl; X¹ is H, fluoro, chloro, bromo, amino, cyano or nitro, which is attached to the 5-ring position of the benzimidazole ring system; and Y is -CH=CH-.

Preferred individual compounds of this invention are:

(E)-2-(4-fluorostyryl)-1-phenyl-1*H*-benzimidazole;
 (E)-2-(2-fluorostyryl)-1-phenyl-1*H*-benzimidazole hydrochloride;
 (E)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-amino-1-phenyl-2-styryl-1*H*-benzimidazole dihydrochloride;
 (E)-5-bromo-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-cyano-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-2-(2-cyclohexylvinyl)-1-phenyl-1*H*-benzimidazole;
 (E)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole hydrochloride; and
 (E)-1-phenyl-2-[2-(2-pyridyl)vinyl]-1*H*-benzimidazole.

Particularly preferred individual compounds are:

(E)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-cyano-1-phenyl-2-styryl-1*H*-benzimidazole; and
 (E)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole hydrochloride.

Preferred pharmaceutical compositions of this invention comprise those compounds of the formula (I), wherein **Ar** is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl selected from pyridyl, pyrrolyl and oxazolyl; **X**² and **X**³ are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; **X**¹ is H, halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkyl, amino, C₁₋₄ alkylamino, cyano or nitro; 1 is 0 or 1; and m and n are independently 0 or 1.

More preferred pharmaceutical compositions of this invention comprise those compounds of the formula (I), wherein **Ar** is phenyl or C₃₋₈ cycloalkyl; **X**² and **X**³ are independently, halo, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; **X**¹ is H, halo, amino, cyano or nitro, which is attached to 5- or 6-ring position of the benzimidazole ring system; and **Y** is -CR¹=CR²-, wherein **R**¹ and **R**² are independently H or methyl.

Furthermore preferred pharmaceutical compositions of this invention comprise those compounds of the formula (I), wherein **Ar** is phenyl, cyclopentyl or cyclohexyl; **X**¹ and **X**³ are independently, fluoro, methylthio, methylsulfinyl or methylsulfonyl; **X**¹ is H, fluoro, chloro, bromo, amino, cyano or nitro, which is attached to the 5-ring position of the benzimidazole ring system; and **Y** is -CH=CH-.

Preferred individual compounds to be contained in the pharmaceutical compositions are:

(E)-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-2-(4-fluorostyryl)-1-phenyl-1*H*-benzimidazole;
 (E)-2-(2-fluorostyryl)-1-phenyl-1*H*-benzimidazole hydrochloride;
 (E)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-amino-1-phenyl-2-styryl-1*H*-benzimidazole dihydrochloride;
 (E)-5-bromo-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-cyano-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-2-(2-cyclohexylvinyl)-1-phenyl-1*H*-benzimidazole;
 (E)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole hydrochloride; and
 (E)-1-phenyl-2-[2-(2-pyridyl)vinyl]-1*H*-benzimidazole.

Particularly preferred individual compounds to be contained in the pharmaceutical compositions of this invention are:

(E)-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-cyano-1-phenyl-2-styryl-1*H*-benzimidazole; and
 (E)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole hydrochloride.

The compounds of the formula (1) of this invention can be administered via either the oral, parenteral or topical routes to mammals. In general, these compounds are most desirably administered to humans in doses ranging from 0.01 mg to 100 mg per kg of body weight per day, although variations will necessarily occur depending upon the weight, sex and condition of the subject being treated, the disease state being treated and the particular route of administration chosen. However, a dosage level that is in the range of from 0.1 mg to 10 mg per kg of body weight per day, single or divided dosage is most desirably employed in humans for the treatment of abovementioned diseases.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the above routes previously indicated, and such administration can be carried

out in single or multiple doses. More particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, trochees, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents, etc. More-
 5 over, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging 5% to 70% by weight, preferably 10% to 50% by weight.

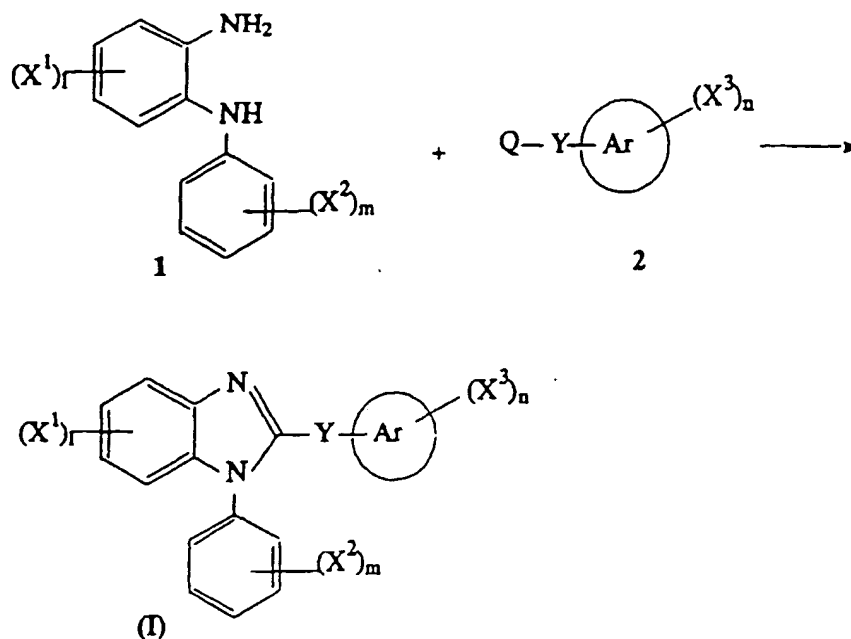
For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type
 10 may also be employed as fillers in gelatine capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH > 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art. Additionally, it is also possible to administer the compounds of the present
 20 invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

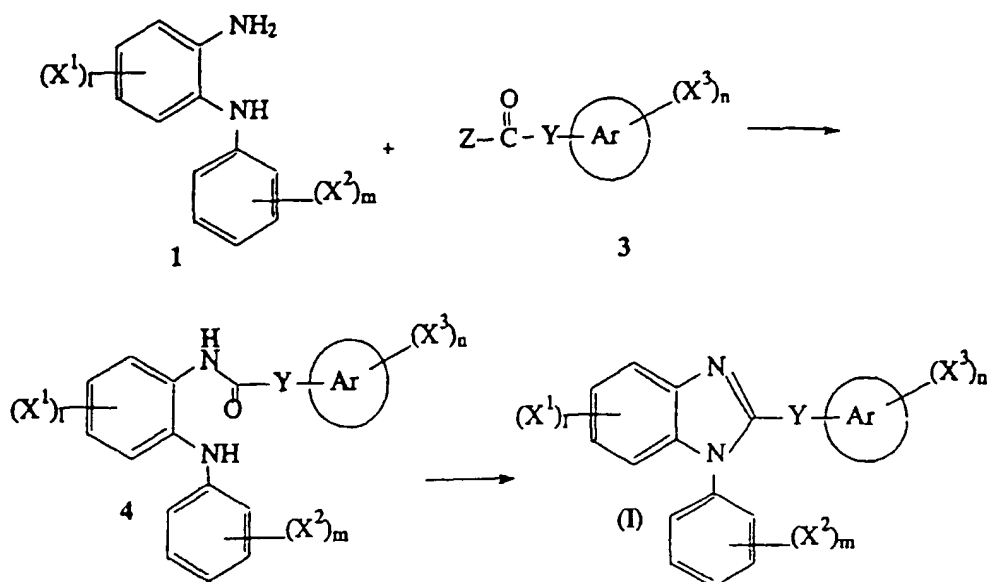
General Synthesis

A compound of formula (I) may be prepared by any synthetic procedure applicable to structure-related compounds known to those skilled in the art. The following representative examples as described in Schemes I-VII are illustrative of the invention in which, unless otherwise stated, Ar, X¹, X², X³ and Y are as defined herein before. For the synthesis of compounds of related-structure to compounds of the present invention, see "Benzimidazoles and Congeneric Tri-
 30 cyclic Compounds" in *Heterocyclic Compounds*, Vol. 40, Preson, P. N. Ed., John Wiley & Sons, NY, 1981.

Scheme I



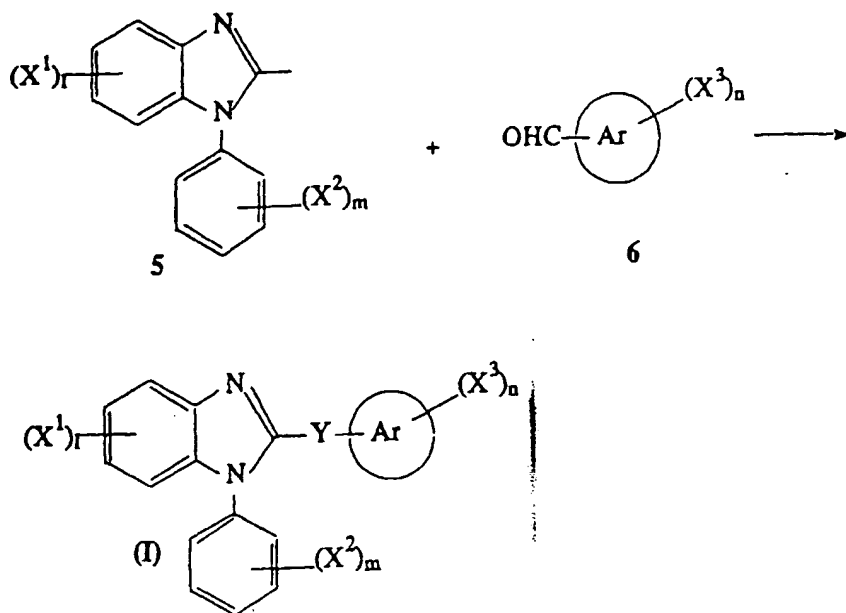
For example, the compound of formula (I) may be prepared according to the reaction outlined in Scheme I. In the instant example, a phenylenediamine compound of formula 1 is reacted with a compound of formula 2 wherein the group Q is a residue of a carboxylic acid, carboxylic acid ester, carboxamide, carboxylic acid anhydride, carboxylic acid chloride, orthoester, imino ether, a carbaldehyde or the like. The reaction may be conducted in the presence or absence of a reaction inert solvent. Preferred reaction inert solvents include benzene, toluene, xylene, pyridine, 1,2-dichloroethane, o-dichlorobenzene, nitrobenzene and dichloromethane. Preferably, the reaction is conducted in the presence of a promoter such as hydrochloric acid, polyphosphoric acid, phosphorous pentoxide, phosphorous oxychloride, polyphosphoric acid ethyl ether, polyphosphoric acid trimethylsilyl ether, *p*-toluenesulfonic acid, zinc (II) chloride or the like. When a compound of formula 2 is carboxaldehyde, the reaction may be conducted in the presence of an oxidant such as cupric acetate, chloranil, or the like. Reaction temperatures are preferably in the range of -40 °C to 250 °C, usually in the range of 20 °C to 200 °C, but if necessary, lower or higher temperature can be employed. Reaction time may vary, in general, from 5 minutes to 6 days, preferably from 20 minutes to 1 day. Alternatively, the reaction may be conducted in a sealed tube or an autoclave at medium (1-10 kg/cm²) to high pressure (20-200 kg/cm²) to accelerate it, preferably in the range of 2 to 150 kg/cm².

Scheme II

Alternatively, the compounds of formula (I) may be prepared by a two step procedure from phenylenediamine compounds of formula 1 via the (*N*-acylamino)phenylamine compounds of formula 4 as shown in Scheme II. In the first step, a phenylenediamine compound of formula 1 is reacted with a compound of formula 3, wherein Z is selected from halo, $-\text{OH}$, $-\text{OR}$ (R is C_{1-4} alkyl), $-\text{NH}_2$, and $-\text{OC}(\text{O})\text{Y}-\text{Ar}-(\text{X}^3)_n$, by conventional methods known to those skilled in the art to form amides of formula 4. For example, when a compound of formula 3 is carboxylic acid (i.e. Z is OH), the reaction is preferably conducted in the presence of a coupling reagent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide (WSC), *N,N'*-dicyclohexylcarbodiimide (DCC), carbonyldiimidazole, cyanophosphonic acid diethyl ester or the like. Preferred reaction-inert solvents include acetone, acetonitrile, dichloromethane, *N,N*-dimethylformamide, *N*, *N*-dimethylacetamide, dimethylsulfoxide, dioxane, tetrahydrofuran and pyridine.

In next step, the compounds of formula (I) are provided by cyclization of the compounds of formula 4. The reaction may be conducted in the presence or absence of a reaction inert solvent. Preferred reaction inert solvents include benzene, toluene, xylene, pyridine, 1,2-dichloroethane, *o*-dichlorobenzene, nitrobenzene, dichloromethane and ethanol. Preferably, the reaction is conducted in the presence of a promoter such as of hydrochloric acid, polyphosphoric acid, phosphorous pentoxide, phosphorous oxychloride, polyphosphoric acid ethyl ether, polyphosphoric acid trimethylsilyl ether, thionyl chloride, *p*-toluenesulfonic acid, or the like. Alternatively, the cyclization reaction may be performed under Mitsunobu-type reaction conditions, for example, in the presence of triphenylphosphine and diethyl azodicarboxylate. Reaction temperatures are preferably in the range of -40°C to 250°C , usually in the range of 20°C to 200°C , but if necessary, lower or higher temperature can be employed. Reaction time may vary, in general, from 5 minutes to 6 days, preferably from 20 minutes to 1 day.

Scheme III



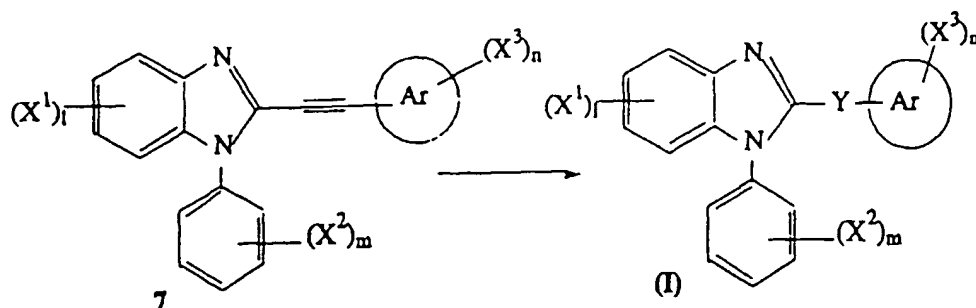
25 In another embodiment, the compounds of formula (I) wherein Y is C(H)=C(H) may be prepared as shown in Scheme III. Thus, 2-methylbenzimidazole compounds of formula 5 are reacted with aldehydes of formula 6 in the presence or absence of base. When the said reaction is conducted in the absence of base, the reaction is preferably performed in a sealed tube or an autoclave at medium (1-10 kg/cm²) to high pressure (20-200 kg/cm²), preferably in the range of 2 to 150 kg/cm². The reaction may be conducted in the presence or absence of a reaction inert solvent.

30 Preferred reaction inert solvents include benzene, toluene, xylene, chlorobenzene, nitrobenzene, acetic acid, acetic anhydride and the like. Reaction temperatures are generally in the range of -100 °C to 250 °C, preferably in the range of 20 °C to 200 °C, but if necessary, lower or higher temperature can be employed. Reaction time may vary, in general, from 5 minutes to a day, preferably from 20 minutes to 5 hours, however shorter or longer reaction times if necessary can be employed. When the said reaction is conducted in the presence of base, reaction temperatures are generally

35 in the range of -100 °C to 250 °C, preferably in the range of -80 °C to 20 °C, but if necessary, lower or higher temperature can be employed. Preferred reaction inert solvents include THF, benzene, toluene and xylenes. Reaction time may vary, in general, from 5 minutes to one day, preferably from 20 minutes to 5 hours, however shorter or longer reaction time, if necessary, can be employed. Preferred bases include, for example, an alkali or alkaline earth metal hydroxide, alkoxide, carbonate or hydride, such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide,

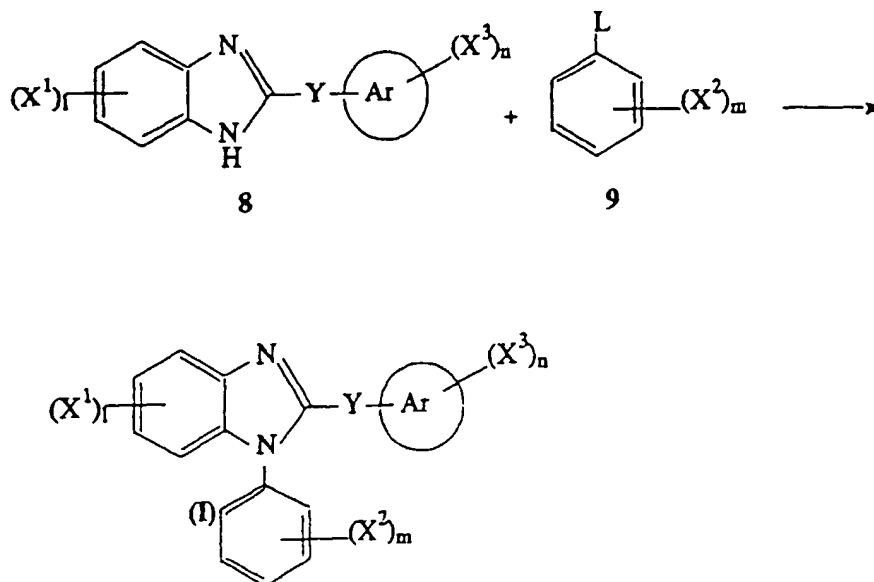
40 potassium *tert*-butoxide, sodium carbonate, potassium carbonate, sodium hydride or potassium hydride; an amine such as triethylamine, diisopropylamine, diisopropylethylamine, piperidine or dimethylaminopyridine; and an alkyl lithium such as *n*-butyl lithium, *sec*-butyl lithium, *tert*-butyl lithium, methyl lithium or lithium diisopropylamide.

45 Scheme IV



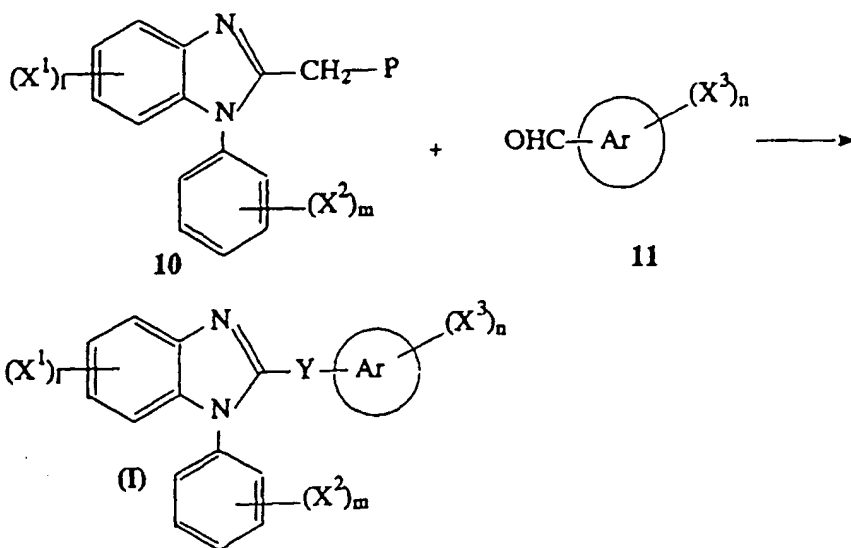
In another embodiment, the compounds of formula (I) wherein Y is C(H)=C(H) may be prepared by partial hydrogenation of a compound of formula (I) wherein Y is C≡C as depicted in Scheme IV. Preferred catalysts include, for example, nickel-based catalysts such as P-2 nickel and nickel boride (Choi, J.; Yoon, N. *M. Tetrahedron Lett.*, 1996, 37, 1057) and palladium-based catalysts such as Lindlar catalyst and Pd/W. Preferred reaction-inert solvents include, for example, water, methanol, ethanol, acetone, acetonitrile, ethyl acetate, dichloromethane, dioxane, tetrahydrofuran, diethyl ether and diisopropyl ether. Reaction temperatures are preferably in the range of -40 °C to 200 °C, usually in the range of 20 °C to reflux temperature of solvent, but if necessary, lower or higher temperature can be employed. Reaction time is in general from 5 minutes to 6 days, preferably from 100 minutes to 5 days.

Scheme V

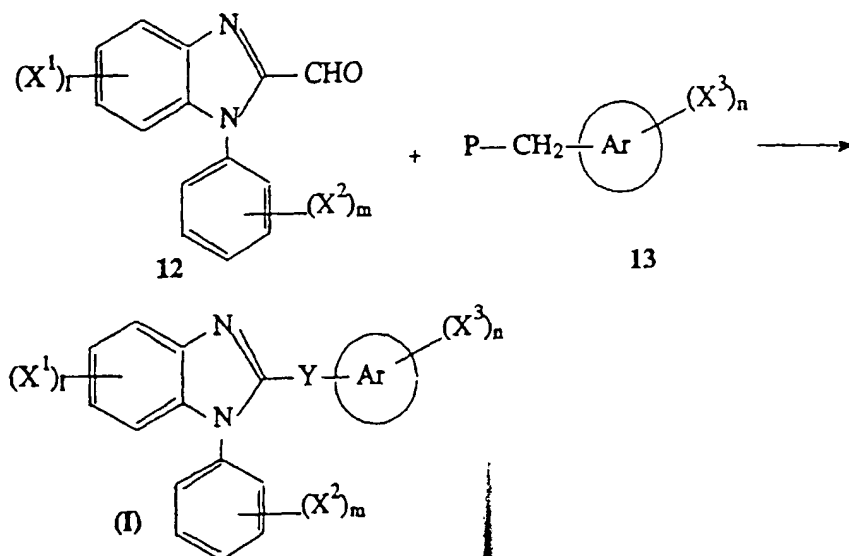


The compounds of formula (I) may also be prepared by reacting a compound of formula 8 with a compound of formula 9 according to the procedure outlined in Scheme V. In Scheme V, the compound of formula 8 may be synthesized by any of the methods described in Schemes I to IV herein before. The group L of the compounds of formula 9 is selected from suitable displaceable groups, for example, halo such as fluoro, chloro, bromo or iodo, and sulfonyloxy such as trifluoromethanesulfonyloxy, methanesulfonyloxy or *p*-toluenesulfonyloxy, all readily accessible by conventional methods known to those skilled in the art. Preferably, the instant reaction is conducted in the presence of a suitable base, for example, an alkali or alkaline earth metal hydroxide, alkoxide, carbonate, or hydride, such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, potassium *tert*-butoxide, sodium carbonate, potassium carbonate, sodium hydride or potassium hydride, or in the presence of an organic base an amine such as triethylamine, diisopropylethylamine diisopropylamine, or dimethylaminopyridine. Preferred reaction-inert solvents include acetone, acetonitrile, dichloromethane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulfoxide, dioxane, tetrahydrofuran and pyridine. Reaction temperatures are preferably in the range of -40 °C to 200 °C, usually in the range of 20 °C to reflux temperature of solvent, but if necessary, lower or higher temperature can be employed. Reaction time is in general from 5 minutes to 6 days, preferably from 30 minutes to 5 days. Conveniently, the reaction may be conducted in the presence of a suitable catalyst, for example, tetrakis(triphenylphosphine)-palladium, bis(triphenylphosphine)palladium (II) chloride, copper (0), cuprous chloride, cuprous oxide, cuprous iodide, cuprous bromide or cuprous chloride.

Scheme VI



Scheme VII



Alternatively, the compounds of formula (I) wherein Y is C(H)=C(H) may be prepared by the reaction of a suitable aldehyde with a suitable phosphonium (Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* 1989, 89, 863) or a dialkyl phosphonate salt (Seguineau, ; Villieras, *Tetrahedron Lett.* 1988, 29, 477) as shown in Schemes VI and VII, wherein P is a suitable phosphonium or dialkyl phosphonate salt. For appropriate references, see DE1939809A.

The starting material of formulae 1, 2, 3, 4, 5, 6, 9, 10, 11, 12 and 13 may be obtained by conventional procedures known to those skilled in the art. The preparation of such starting materials is described within the accompanying nonlimiting examples which are provided for the purpose of illustration only. Alternatively, requisite starting materials may be obtained by analogous procedures, or modifications thereof described hereinafter.

The products which are addressed in the aforementioned general synthesis and illustrated in the experimental examples herein may be isolated by standard methods and purification can be achieved by conventional means known to those skilled in the art, such as distillation, recrystallization and chromatography techniques.

EP 0 846 689 A1

The compounds of the present invention which contain one or more double bonds and/or asymmetric centers are capable of existing in various stereoisomeric forms. All such individual forms, and mixtures thereof, are included within the scope of the invention. The various isomers can be obtained by standard methods. For example, *cis/trans* mixtures can be separated into the individual stereoisomers by stereoselective synthesis, or by separation of the mixtures by fractional crystallization or chromatography techniques.

A number of the compounds of the present invention are capable of forming addition salts with inorganic and organic acids. The pharmaceutically acceptable acid salts of the compounds of the present invention are those which form non-toxic addition salts, such as, but not limited to, the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or acetate, fumarate, tartrate, succinate, maleate, glucuronate, saccharate, benzoate, methanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts.

The compounds of the invention which have also acidic groups are capable of forming base salts with various pharmaceutically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and particularly, the sodium or potassium salts. These salts are all prepared by conventional techniques. For example, these salts can be easily prepared by treating the aforementioned compounds with an aqueous solution containing the desired pharmaceutically acceptable cation, and then evaporating the resulting solution to dryness, preferable under reduce pressure. Alternatively, they may be also be prepared by mixing together with a lower alkoxide, and then evaporating the resulting solution to dryness in the same manners as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum production of yields of the desired final product.

Also included within the scope of this invention are bioprecursors (also called pro-drugs) of the compounds of the formula (I). A bioprecursor of a compound of the formula (I) is a chemical derivative thereof which is readily converted back into the parent compound of the formula (I) in biological systems. In particular, a bioprecursor of a compound of the formula (I) is converted back to the parent compound of the formula (I) after the bioprecursor has been administered to, and absorbed by, a mammalian subject, e.g., a human subject. For example, it is possible to make a bioprecursor of the compound of the formula (I) in which X' is a hydroxy group by making an ester of the hydroxy group. Typical esters are simple alkanoate esters, such as acetate, propionate and butyrate. In addition, when X' is a hydroxy group, bioprecursors can be made by converting the hydroxy group to an acyloxymethyl derivative (e.g., a pivaloyloxymethyl derivative) by reaction with an acyloxymethyl halide (e.g., pivaloyloxymethyl chloride). When the compounds of the formula (I) of this invention may form solvates such as hydrates, such solvates are included within the scope of this invention.

Biological evaluation

The activity of the compounds of the formula (I) of the present invention, is demonstrated by the following assays. Human umbilical vein endothelial cells (HUVEC), which was characterized by positive staining with von Willibrand's factor and an uptake of acetylated low-density lipoproteins, was purchased from Morinaga Bioscience Lab., Yokohama, Japan. HUVEC was maintained in E-GM UV (from Kurashikibouseki Co., Neyagawa, Japan) in 5% CO₂/95% air at 37 °C. PGE₂, TXB₂ and 6-keto-PGF_{1α} were from Cayman Chemical Co. (Ann Arbor, USA). Recombinant human interleukin-1β (hIL-1β) was from R&D Systems (Minneapolis, USA). RIA kits for PGE₂, TXB₂ and 6-keto-PGF_{1α} were from Amersham (Tokyo, Japan). Indomethacin and other reagents were from Sigma Chemical Co. (St. Louis, USA). Dexamethasone (decadron[Trademark]) was from Banyu Pharmaceutical Co. (Tokyo, Japan). Vacutainer[Trademark] was from Becton Dickinson (Bedford, USA). Male Sprague-Dawley rats were purchased from Charles River (Hino, Japan).

Human cell-based COX-1 assay

Human cell based COX-1 assay was carried out essentially according to a previously described procedure (Grossman *et al.*, *Inflam. Res.*, **44**, 1995, 253). Human peripheral blood was obtained from healthy volunteers using Vacutainer [Trademark] containing 1/10 volume of 3.8% sodium citrate solution. After centrifugation, platelet-rich plasma was washed with 0.14 M sodium chloride containing 12 mM Tris-HCl (pH 7.4) and 1.2 mM EDTA. Resulting platelet was washed with 20 mM Hepes-Ca²⁺ free Hanks buffer containing 0.2% BSA. Washed human platelet (WHP) was suspended at the concentration of 2.85 x 10⁷ cells/ml in the above buffer and stored at room temperature until use. Immediately before assay, 10 μl of 12.6 mM CaCl₂ was added to 70 μl WHP suspension (2.0 x 10⁷ cells/ml in a 96-well U bottom plate). Platelets were incubated with a test compound dissolved in DMSO (final concentration less than 0.01%) and A23187 (final 10 μM) at 37 °C for 15 min. Reaction was stopped by addition of EDTA (final 7.7 mM). TXB₂ in the supernatant was quantitated by RIA.

Human cell-based COX-2 assay

Human cell based COX-2 assay was carried out essentially according to a previously described procedure (Moore *et al.*, *Inflam. Res.*, **45**, 1996, 54). Confluent HUVEC in a 96-well plate were washed with 100 μ l of RPMI 1640 containing 2% FCS and stimulated with hIL-1 β (final 300 U/ml) at 37 °C for 24 hr. HUVEC pretreated with hIL-1 β were washed with 20 mM Hepes-Hanks buffer containing 0.2% BSA. The incubation was initiated in 100 μ l of the *above* buffer, A23187 (final 30 μ M) and a test compound dissolved in DMSO (final concentration less than 0.01%) at 37 °C for 15 min. 6-Keto-PGF1 α , a stable metabolite of PGI $_2$, in the supernatant was quantitated by RIA.

Carrageenan induced foot edema in rats

Male Sprague-Dawley rats (5 weeks old), fasted overnight, were injected intradermally λ -carrageenan (0.1 ml of 1% w/v suspension in saline) into right *hind* paw as previously reported. (Winter *et al.*, *Proc. Soc. Exp. Biol. Med.*, **111**, 1962, 544; Lombardino *et al.*, *Arzneim. Forsch.*, **25**, 1975, 1629) Foot volume was measured by water displacement using a plethysmometer (Unicom Co., Yachiyo, Japan) before and 3 h after carrageenan injection. Test compounds were *suspended* in 0.1% w/v methylcellulose and dosed orally in a volume of 2.5 ml per 100 g body weight 1 h before carrageenan injection.

Measurement of PGE $_2$ in inflammatory site and stomach in rats

Determination of PGE $_2$ synthesized in the inflammatory site was carried essentially according to a previously described method (Opas *et al.*, *Biochem. Pharmacol.*, **36**, 1987, 547). Foot edema in male Sprague-Dawley rats (5 weeks old) was induced by subplanter injection of 0.1 ml of 1% w/v λ -carrageenan suspension. Animals were sacrificed by cervical dislocation 3 h following carrageenan injection. The foot was amputated, frozen in liquid nitrogen and stored at -80 °C until analysis. The stomach of these animals were excised, frozen in liquid nitrogen and stored at -80 °C until analysis. The frozen foot was crushed, mixed with 7 ml of ethanol containing 10 μ g/ml of indomethacin, pulverized in a Waring blender and clarified by centrifugation at 3,000 r.p.m. for 10 min at 4 °C. The frozen stomach was mixed with 7 ml of ethanol containing 10 μ g/ml of indomethacin, homogenized by polytrone and clarified by centrifugation at 3,000 r.p.m. for 10 min at 4 °C. PGE $_2$ was extracted by a Sep-Pak(Trademark) C18 cartridge (from Waters, Milford, USA) and dried in vacuum. Samples were diluted to a final volume of 0.5 ml with assay buffer (PBS containing 0.1% w/v gelatin) and the level of PGE $_2$ was quantitated by RIA according to Amersham protocol. Test compounds were *suspended* in 0.1% w/v methylcellulose and dosed 1 h before carrageenan injection. Dexamethasone was dissolved in saline and administered subcutaneously 3 h before carrageenan injection.

Gastric ulceration in rats

The gastric ulcerogenicity of test compound was assessed using previously described standard method (Ezer *et al.*, *J. Pharm. Pharmacol.*, **28**, 1976, 655). Male Sprague-Dawley rats (5 weeks old), fasted overnight, were *used* in this assay. Compounds were *suspended* in 0.1% w/v methylcellulose and dosed orally in a volume of 1.0 ml per 100 g body weight. Six hours after compound administration, the animals were sacrificed by cervical dislocation. The stomach was removed and inflated with 10 ml of 1% formalin solution. The stomach was opened by cutting along the greater curvature and the incidence of ulcer including ecchymosis was evaluated by all-or-none method. Rats refrained from water during experiments. The half-ulcerogenic dose (UD $_{50}$) value, i.e., dose required to induce at least one gastric lesion or one hemorrhagic erosion in 50% of the animals tested, was calculated by non-linear equation; % Control = 100/(1 + [Dose]/UD $_{50}$).

Data Analysis

A statistical program package SYSTAT for Macintosh (SYSTAT, INC.) was used. Differences between compound treated group and control group were tested for using ANOVA. The IC $_{50}$ or ED $_{50}$ value was calculated from the equation for the log-linear regression line of concentration (dose) versus percent inhibition.

Most compounds prepared in the Working Examples as described herein after were tested by these methods, and showed IC $_{50}$ values of 0.01 μ M to 1.0 μ M with respect to inhibition of COX-2.

COX-2 selectivity can be determined by ratio in terms of IC $_{50}$ value of COX-1 inhibition to COX-2 inhibition. In general, it can be said that a compound showing a COX-2/COX-1 inhibition ratio of more than 2 has good COX-2 selectivity.

Compounds prepared in Examples 1, 14, 17 and 21 as described below showed COX-2/COX-1 inhibition ratio of more than 10.

The following examples contain detailed descriptions of the methods of the preparation of compounds of formula (I). These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction in the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise noted.

Examples and Preparations

The present invention is illustrated by the following examples and preparations. However, it should be understood that the invention is not limited to the specific details of these examples and preparations. Melting points were taken with a Buchi micro melting point apparatus and *uncorrected*. Infrared Ray absorption spectra (IR) were measured by a Shimadzu infrared spectrometer (IR-470). ¹H and ¹³C nuclear magnetic resonance spectra (NMR) were measured in CDCl₃ by a JEOL NMR spectrometer (JNM-GX270, 270MHz) unless otherwise indicated and peak positions are expressed in parts per million (ppm) *downfield from tetramethylsilane*. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

Example 1

(E)-1-Phenyl-2-styryl-1H-benzimidazole

To a stirred solution of *N*-phenyl-*o*-phenylenediamine (1.0 g, 5.4 mmol) in toluene (30 ml) was added cinnamoyl chloride (0.90 g, 5.4 mmol) in small portions and the mixture was heated under reflux overnight. The reaction mixture was cooled and poured into saturated aqueous sodium bicarbonate solution (50 ml) and extracted with ethyl acetate (100 ml). The organic extract was washed consecutively with water (50 ml) and brine (50 ml), dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 150 g; *n*-hexane/ethyl acetate (4/1)) to give pink solids. Recrystallization from diisopropyl ether afforded 1.35 g (84%) of the titled compound as white solids. This compound is used in a pharmaceutical composition.

MW: 296.37

mp: 133.8-134.5 °C

¹H-NMR (CDCl₃) δ: 7.97 (1 H, d, J = 15.8 Hz), 7.84 (1 H, d, J = 8.1 Hz), 7.67-7.56 (3 H, m), 7.50-7.42 (4 H, m), 7.38-7.16 (6 H, m), 6.85 (1 H, d, J = 15.8 Hz)

Example 2

(E)-2-(4-Fluorostyryl)-1-phenyl-1H-benzimidazole

The titled compound was prepared from *N*-phenyl-*o*-phenylenediamine and *p*-fluorocinnamoyl chloride (Gene, J. T.; McLeod, R. S. *Can. J. Chem.*, **53**, 1975, 513) according to the preparation of (E)-1-phenyl-2-styryl-1H-benzimidazole (example 1).

MW: 314.37

mp: 108.7-109.5 °C

¹H-NMR (CDCl₃) δ: 7.93 (1 H, d, J = 16.1 Hz), 7.83 (1 H, d, J = 8.1 Hz), 7.68-7.56 (3 H, m), 7.49-7.40 (4 H, m), 7.33 (1 H, ddd, J = 7.7, 7.7, 1.8 Hz), 7.27-7.16 (2 H, m), 7.07-6.98 (2 H, m), 6.76 (1 H, d, J = 16.1 Hz)

Example 3

(E)-2-(3-Fluorostyryl)-1-phenyl-1H-benzimidazole hydrochloride

(E)-2-(3-Fluorostyryl)-1-phenyl-1H-benzimidazole was prepared from *N*-phenyl-*o*-phenylenediamine and *m*-fluorocinnamoyl chloride (Gerig, J. T.; McLeod, R. S. *Can. J. Chem.*, **53**, 1975, 513) according to the preparation of (E)-1-phenyl-2-styryl-1H-benzimidazole (example 1). The free base was *dissolved* into methanol, treated with a 10% methanol solution of *hydrogen* chloride and concentrated to dryness. The residue was recrystallized from diisopropyl ether to give the titled compound as white needles.

MW: 350.83

mp: 236.0-243.0 °C

¹H-NMR (DMSO-d₆) δ: 8.27 (1 H, d, J = 16.8 Hz), 7.90 (1 H, d, J = 8.1 Hz), 7.82-7.70 (5 H, m), 7.63-7.44 (5 H, m), 7.38-7.25 (2 H, m), 7.02 (1 H, d, J = 16.8 Hz)

Example 4

(E)-2-(2-Fluorostyryl)-1-phenyl-1H-benzimidazole hydrochloride

The titled compound was prepared from *N*-phenyl-*o*-phenylenediamine and *o*-fluorocinnamoyl chloride (Gerig, J. T.; McLeod, R. S. Can. J. Chem., 53, 1975, 513) according to the preparation of (E)-2-(3-fluorostyryl)-1-phenyl-1H-benzimidazole hydrochloride (example 3).

MW: 350.83

mp: 225.0-228.0 °C

¹H-NMR (DMSO-d₆) δ: 8.27 (1 H, d, J = 16.5 Hz), 7.91 (1 H, d, J = 8.1 Hz), 7.82-7.69 (6 H, m), 7.63-7.46 (3 H, m), 7.39-7.25 (3 H, m), 7.00 (1 H, d, J = 16.5 Hz)

Example 5

(E)-2-(4-Methylthiostyryl)-1-phenyl-1H-benzimidazole

The titled compound was prepared from *N*-phenyl-*o*-phenylenediamine and *p*-methylthiocinnamoyl chloride (Miller, R. D.; Reiser, O. J. Heterocycl. Chem., 30, 1993, 755) according to the preparation of (E)-1-phenyl-2-styryl-1H-benzimidazole (example 1).

MW: 342.47

mp: 175.7-179.5 °C

¹H-NMR (CDCl₃) δ: 7.91 (1 H, d, J = 16.1 Hz), 7.82 (1 H, d, J = 7.7 Hz), 7.67-7.55 (3 H, m), 7.48-7.15 (9 H, m), 6.79 (1 H, d, J = 16.1 Hz), 2.47 (3 H, s)

Example 6

(E)-2-(4-Methylsulfinylstyryl)-1-phenyl-1H-benzimidazole hydrochloride

To a stirred solution of (E)-2-(4-methylthiostyryl)-1-phenyl-1H-benzimidazole (0.31 g, 0.92 mmol) in a mixture of methanol (10 ml) and water (10 ml) cooled to 0 °C was added sodium periodate (0.21 g, 1.0 mmol). The ice bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (50 ml) and extracted with ethyl acetate (100 ml). The organic extract was washed consecutively with water (50 ml) and brine (50 ml), dried (sodium sulfate) and concentrated in vacuo. The residual solids were purified by column chromatography (silica gel, 100 g; ethyl acetate) to give brown solids. The solids were treated with a 10% methanol solution of hydrogen chloride (5 ml) and volatiles were removed in vacuo. Recrystallization of the residue from ethanol afforded 0.18 g (50%) of the titled compound as yellow solids.

MW: 394.93

mp: 192.9-193.8 °C

¹H-NMR (CDCl₃) δ: 7.98 (1 H, d, J = 16.1 Hz), 7.84 (1 H, d, J = 8.1 Hz), 7.69-7.56 (7 H, m), 7.48-7.42 (2 H, m), 7.38-7.17 (3 H, m), 6.93 (1 H, d, J = 16.1 Hz), 2.71 (3 H, s)

Example 7

(E)-2-(4-Methylsulfonylstyryl)-1-phenyl-1H-benzimidazole

To a stirred solution of (E)-2-(4-methylthiostyryl)-1-phenyl-1H-benzimidazole (0.60 g, 1.75 mmol) in a mixture of methanol (5 ml), tetrahydrofuran (5 ml) and water (5 ml) was slowly added OXONE (Trademark) (1.63 g, 2.65 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (30 ml) and the aqueous mixture was extracted with ethyl acetate (100 ml). The organic extract was washed consecutively with water (50 ml) and brine (50 ml), dried (sodium sulfate) and concentrated in vacuo. The residual solids were purified by column chromatography (silica gel, 100 g; *n*-hexane/ethyl acetate (1/1)) to give brown solids. Recrystallization from ethyl acetate afforded 0.24 g (36%) of the titled compound as light yellow

solids.

MW: 374.47

mp: 168.6-169.5°C

¹H-NMR (CDCl₃) δ: 8.03 (1 H, d, J = 15.8 Hz), 7.93-7.82 (3 H, m), 7.68-7.59 (5 H, m), 7.49-7.44 (2 H, m), 7.40-7.19 (3 H, m), 6.97 (1 H, d, J = 15.8 Hz), 3.05 (3 H, s)

Example 8

(E)-2-(β-Methylstyryl)-1-phenyl-1H-benzimidazole hydrochloride

To a stirred solution of *N*-phenyl-*o*-phenylenediamine in toluene (50 ml) was added a solution of 2-methyl-3-phenylacryloyl chloride (1.81 g, 10 mmol, Watanabe, T.; Hayashi, K.; Yoshimatsu, S.; Sakai, K. J. Med. Chem., 23, 1980, 50) in toluene (20 ml) at room temperature over 15 min. The resulting mixture was stirred at room temperature for 10 min and then heated to reflux removing water azeotropically using a Dean-Stark apparatus for 12 h. After cooling, volatiles were evaporated off and the residue was dissolved into xylenes (75 ml). To the solution was added *p*-toluenesulfonic acid monohydrate (0.40 g, 2.1 mmol) and the mixture was heated to reflux removing water azeotropically. After 9 h, the reaction mixture was concentrated to dryness and the residue was dissolved into a mixture of ethyl acetate (100 ml) and saturated aqueous sodium bicarbonate solution (100 ml). The organic layer was separated and washed with brine (100 ml), dried (magnesium sulfate) and concentrated to dryness. The residue was dissolved into hot toluene and the solution was treated with active carbon. After filtration, the filtrate was concentrated to dryness. The residue was triturated with *n*-hexane to give 1.61 g (52%) of (*E*)-2-(β-methylstyryl)-1-phenyl-1H-benzimidazole as pink solids. The free base was dissolved into methanol (15 ml), treated with a 10% methanol solution of hydrogen chloride (15 ml) and concentrated to dryness. Recrystallization from 2-propanol afforded 1.52 g of the titled compound as off-white solids.

MW: 346.86

mp: 222.0-225.0°C

¹H NMR ((DMSO-*d*₆) δ: 7.98-7.93 (1 H, m), 7.79-7.51 (7 H, m), 7.48-7.29 (6 H, m), 7.18 (1 H, br. s), 2.13 (3H, d, J = 1.5 Hz)

Example 9

(E)-6-Chloro-1-phenyl-2-styryl-1H-benzimidazole

The titled compound was prepared from 4-chloro-2-anilinoaniline (Ernst, O. Chem. Ber., 23, 1890, 3423) and cinnamoyl chloride according to the preparation of (*E*)-1-phenyl-2-styryl-1H-benzimidazole (example 1).

MW: 330.82

mp: 163.1-164.2°C

¹H-NMR (CDCl₃) δ: 7.95 (1 H, d, J = 16.1 Hz), 7.73 (1 H, d, J = 8.8 Hz), 7.67-7.58 (3 H, m), 7.49-7.41 (4 H, m), 7.38-7.25 (4 H, m), 7.17 (1 H, d, J = 1.8 Hz), 6.81 (1 H, d, J = 16.1 Hz)

Example 10

(E)-5-Chloro-1-phenyl-2-styryl-1H-benzimidazole

The titled compound was prepared from 5-chloro-2-anilinoaniline (Ullmann, F. Justus Liebigs Ann. Chem., 332, 1904, 82) and cinnamoyl chloride according to the preparation of (*E*)-1-phenyl-2-styryl-1H-benzimidazole (example 1).

MW: 330.82

mp: 169.5-170.5°C

¹H-NMR (CDCl₃) δ: 7.96 (1 H, d, J = 16.1 Hz), 7.80 (1 H, d, J = 1.8 Hz), 7.68-7.57 (3 H, m), 7.49-7.40 (4 H, m), 7.38-7.29 (3 H, m), 7.19 (1 H, dd, J = 8.8, 1.8 Hz), 7.09 (1 H, d, J = 8.8 Hz), 6.81 (1 H, d, J = 16.1 Hz)

Example 11**(E)-1-(4-Fluorophenyl)-2-styryl-1H-benzimidazole hydrochloride**

The titled compound was prepared from *N*-4-fluorophenyl-*o*-phenylenediamine (Elguero, J.; Estopa, C.; Ilavsky, D. J. Chem. Res. Miniprint, 12, 1981, 4237) and cinnamoyl chloride according to the preparation of (*E*)-2-(β -methylstyryl)-1-phenyl-1*H*-benzimidazole hydrochloride (example 8).

MW: 350.83

mp: 257.5-259.0°C

¹H-NMR (DMSO-*d*₆) δ : 8.16 (1 H, d, *J* = 16.1 Hz), 7.90-7.75 (3 H, m), 7.69-7.42 (9 H, m), 7.33 (1 H, d, *J* = 7.7 Hz), 6.93 (1 H, d, *J* = 16.1 Hz)

Example 12**(E)-1-(4-Fluorophenyl)-2-(4-methylthiostyryl)-1H-benzimidazole**

The titled compound was prepared from *N*-4-fluorophenyl-*o*-phenylenediamine and *p*-methylthiocinnamoyl chloride according to the preparation of (*E*)-1-phenyl-2-styryl-1*H*-benzimidazole (example 1).

MW: 360.46

mp: 187.7-188.5°C

¹H-NMR (CDCl₃) δ : 7.91 (1 H, d, *J* = 16.1 Hz), 7.82 (1 H, d, *J* = 7.7 Hz), 7.46-7.11 (11 H, m), 6.73 (1 H, d, *J* = 16.1 Hz), 2.48 (3 H, s)

Example 13**(E)-2-(4-Fluorostyryl)-1-(4-methylthiophenyl)-1H-benzimidazole****1. N-4-Methylthiophenyl-*o*-phenylenediamine**

To a mixture of 2-nitrochlorobenzene (10.0 g, 63.5 mmol) and 4-methylthioaniline (8.84 g, 63.5 mmol) was added potassium fluoride (3.70 g, 63.7 mmol) and the reaction mixture was heated for 30 h at 170 °C with vigorous stirring. The mixture was cooled and directly flash-chromatographed on silica gel (100 g) eluting with *n*-hexane/ethyl acetate (20/1) to give 12.5 g of a brown oil. The oil was dissolved in ethanol (250 ml), 5% palladium on carbon (1.5 g) added and the mixture hydrogenolyzed under medium hydrogen pressure (2.5 kgf/cm²) for 2 h. Catalyst was removed by filtration through a celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 500 g; *n*-hexane/ethyl acetate (4/1)) to give 0.51 g (4%) of *N*-4-methylthiophenyl-*o*-phenylenediamine as black solids.

¹H-NMR (CDCl₃) δ : 7.22 (2 H, d, *J* = 8.4 Hz), 7.10 (1 H, dd, *J* = 7.7, 1.5 Hz), 7.02 (1 H, ddd, *J* = 7.7, 7.7, 1.5 Hz), 6.80 (1 H, dd, *J* = 7.7, 1.5 Hz), 6.76 (1 H, ddd, *J* = 7.7, 7.7, 1.5 Hz), 6.69 (2 H, d, *J* = 8.4 Hz), 5.16 (2 H, br. s), 3.76 (1 H, br. s), 2.43 (3 H, s).

2. (E)-2-(4-Fluorostyryl)-1-(4-methylthiophenyl)-1H-benzimidazole

The titled compound was prepared from *N*-4-methylthiophenyl-*o*-phenylenediamine and *p*-fluorocinnamoyl chloride according to the preparation of (*E*)-1-phenyl-2-styryl-1*H*-benzimidazole (example 1).

MW: 360.46

mp: 106.9-107.9°C

¹H-NMR (CDCl₃) δ : 7.93 (1 H, d, *J* = 16.1 Hz), 7.82 (1 H, d, *J* = 7.7 Hz), 7.49-7.41 (4 H, m), 7.38-7.14 (5 H, m), 7.08-6.98 (2 H, m), 6.74 (1 H, d, *J* = 16.1 Hz), 2.60 (3 H, s)

Example 14**(E)-5-Nitro-1-phenyl-2-styryl-1H-benzimidazole**

The titled compound was prepared from 5-nitro-2-anilinoaniline (Brand, K.; Wild, E. Chem. Ber., 56, 1923, 105)

and cinnamoyl chloride according to the preparation of (*E*)-1-phenyl-2-styryl-1*H*-benzimidazole(example 1).

MW: 341.37

mp: 173.8-174.7°C

¹H-NMR (CDCl₃) δ: 8.72 (1 H, d, J = 2.2 Hz), 8.16 (1 H, dd, J = 8.8, 2.2 Hz), 8.04 (1 H, d, J = 16.1 Hz), 7.72-7.62 (3 H, m), 7.52-7.42 (4 H, m), 7.38-7.31 (3 H, m), 7.22 (1 H, d, J = 8.8 Hz), 6.81 (1 H, d, J = 16.1 Hz)

Example 15

(*E*)-5-Amino-1-phenyl-2-styryl-1*H*-benzimidazole dihydrochloride

Iron powder (0.17 g, 3.1 mmol) and ammonium chloride (18 mg, 0.33 mmol) was added to a solution of (*E*)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole (0.21 g, 0.62 mmol) in ethanol (4 ml) and water (2 ml). The reaction mixture was refluxed for 30 min, the hot reaction mixture filtered through a celite pad and the filtrate was evaporated under reduced pressure. The residue obtained was partitioned between ethyl acetate (50 ml) and saturated aqueous sodium bicarbonate solution (50 ml) and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (50 ml). The combined organic extracts were washed with brine (50 ml), dried (sodium sulfate) and concentrated in vacuo to afford 0.20 g of yellow solids. The solids were treated with a 10% methanol solution of hydrogen chloride (5 ml) and volatiles were removed. Recrystallization of the residue from ethanol afforded 0.14 g (59%) of the titled compound as yellow solids.

MW: 384.31

mp: 200.0-203.0°C

¹H-NMR (CDCl₃) δ: 7.90 (1 H, d, J = 16.1 Hz), 7.67-7.24 (10 H, m), 7.11 (1 H, d, J = 1.8 Hz), 6.99 (1 H, d, J = 8.4 Hz), 6.81 (1 H, d, J = 16.1 Hz), 6.66 (1 H, dd, J = 8.4, 1.8 Hz), 3.71 (2 H, br. s)

Example 16

(*E*)-5-Bromo-1-phenyl-2-styryl-1*H*-benzimidazole

To a stirred solution of (*E*)-5-amino-1-phenyl-2-styryl-1*H*-benzimidazole (0.31 g, 1.0 mmol) in 47% hydrobromic acid (5 ml) and water (2 ml) was added an aqueous (1 ml) solution of sodium nitrite (84 mg, 1.2 mmol) at -5 °C and the reaction mixture was stirred for 10 min at the same temperature. The resultant diazonium salt was added to a solution of copper(I) bromide (0.30 g, 2.0 mmol) in 47% hydrobromic acid (5 ml) cooled to -5 °C and the reaction mixture was stirred for 30 min at 0 °C and for 30 min at room temperature. *N,N,N',N'*-Tetramethylethylenediamine (5ml) and a 4 *N* aqueous solution of potassium hydroxide (30 ml) were added consecutively to the reaction mixture. The mixture was extracted with ethyl acetate (100 ml) and the ethyl acetate extract was washed consecutively with water (50 ml) and brine (50 ml), dried (sodium sulfate) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 50 g; *n*-hexane/ethyl acetate (4/1)) to give white solids. Recrystallization from diisopropyl ether gave 61 mg (16%) of the titled compound as white solids.

MW: 375.27

mp: 164.3-165.5°C

¹H-NMR (CDCl₃) δ: 7.95 (1 H, d, J = 16.1 Hz), 7.95 (1 H, d, J = 1.8 Hz), 7.67-7.56 (3 H, m), 7.49-7.39 (4 H, m), 7.38-7.28 (4 H, m), 7.04 (1 H, d, J = 8.8 Hz), 6.81 (1 H, d, J = 16.1 Hz)

Example 17

(*E*)-5-Cyano-1-phenyl-2-styryl-1*H*-benzimidazole

A mixture of (*E*)-5-bromo-1-phenyl-2-styryl-1*H*-benzimidazole (1.54 g, 4.1 mmol) and copper(I) cyanide (0.82 g, 8.2 mmol) in 1-methyl-2-pyrrolidone (10 ml) was refluxed for 2 h. Then, *N,N,N',N'*-tetramethylethylenediamine (50 ml) was added and the mixture partitioned between ethyl acetate (200 ml) and saturated aqueous sodium bicarbonate solution (200 ml). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (200 ml). The combined organic phase was washed with brine (300 ml), dried (sodium sulfate) and concentrated. The residue was purified by column chromatography (silica gel, 150 g; *n*-hexane/ethyl acetate (3/1)) and obtained solids (1.05 g, 80%) recrystallized from ethyl acetate/diisopropyl ether to afford the titled compound as off white solids.

MW: 321.38

mp: 191.3-192.4°C

¹H-NMR (CDCl₃) δ: 8.12 (1 H, d, J = 1.8 Hz), 8.01 (1 H, d, J = 16.1 Hz), 7.71-7.61 (3 H, m), 7.50-7.42 (5 H, m), 7.38-7.11 (3 H, m), 7.23 (1 H, d, J = 8.4 Hz), 6.80 (1 H, d, J = 16.1 Hz)

Example 18**(E)-1-Phenyl-2-styryl-1H-benzimidazole-5-carboxamide**

To a solution of (E)-5-cyano-1-phenyl-2-styryl-1H-benzimidazole (0.30 g, 0.93 mmol) in 2-methyl-2-propanol (10 ml) was added powdered potassium hydroxide (0.19 g, 2.8 mmol). After stirring 2 h at 80 °C, volatiles were removed in vacuo and the residue was partitioned between ethyl acetate (50 ml) and water (50 ml). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (50 ml). The combined extracts were washed consecutively with water (50 ml) and brine (50 ml), dried (sodium sulfate) and concentrated in vacuo. The residue was recrystallized from ethyl acetate to afford 0.16 g (52%) of the titled compound as white solids.

MW: 339.40

mp: >220°C

¹H-NMR (CDCl₃) δ: 8.24 (1 H, d, J = 1.8 Hz), 7.98 (1 H, d, J = 16.1 Hz), 7.81 (1 H, dd, J = 8.4, 1.8 Hz), 7.69-7.58 (3 H, m), 7.51-7.41 (4 H, m), 7.39-7.29 (3 H, m), 7.23 (1 H, d, J = 8.4 Hz), 6.83 (1 H, d, J = 16.1 Hz), 6.01 (2 H, br. s)

Example 19**(E)-1-Phenyl-2-[2-(3-pyridyl)vinyl]-1H-benzimidazole dihydrochloride**

The titled compound was prepared from N-phenyl-o-phenylenediamine and 3-(3-pyridyl)acryloyl chloride according to the preparation of (E)-2-(3-fluorostyryl)-1-phenyl-1H-benzimidazole hydrochloride (example 3).

3-(3-Pyridyl)acryloyl chloride was obtained as follows. A mixture of 3-(3-pyridyl)acrylic acid and thionyl chloride was heated to reflux under a dry atmosphere for 140 min. Volatiles were removed by evaporation under reduced pressure and obtained 3-(3-pyridyl)acryloyl chloride was used without purification.

MW: 370.28

mp: 270.0-273.0°C

¹H-NMR (DMSO-d₆) δ: 9.10 (1 H, d, J = 1.5 Hz), 7.78 (1 H, dd, J = 6.1, 1.5 Hz), 8.61-8.45 (1 H, m), 8.24 (1H, br. d, J = 16.1 Hz), 7.90-7.77 (7H, m), 7.52 (1 H, ddd, J = 8.4, 7.7, 1.5 Hz), 7.44 (1 H, ddd, J = 8.4, 7.7, 1.5 Hz), 7.32 (1 H, dd, J = 7.7, 1.5 Hz), 7.26 (1 H, d, J = 16.1 Hz)

Example 20**(E)-2-(2-Cyclohexylvinyl)-1-phenyl-1H-benzimidazole**

The titled compound was prepared from N-phenyl-o-phenylenediamine and 3-cyclohexylacryloyl chloride (Amino, Y.; Kawada, K.; Toi, K.; Kumashiro, I.; Fukushima, K. Chem. Pharm. Bull., 11, 1988, 4426) according to the preparation of (E)-1-phenyl-2-styryl-1H-benzimidazole (example 1).

MW: 302.42

mp: 100.0-101.0°C

¹H-NMR (CDCl₃) δ: 7.78 (1 H, br. d, J = 8.1 Hz), 7.64-7.48 (3 H, m), 7.42-7.36 (2 H, m), 7.31-7.13 (3H, m), 7.07 (1 H, dd, J = 15.8, 7.3 Hz), 6.16 (1 H, dd, J = 15.8, 0.5 Hz), 2.20-2.06 (1 H, m), 1.80-1.49 (5 H, m), 1.33-1.08 (5H, m)

Example 21**(E)-2-(2-Cyclopentylvinyl)-1-phenyl-1H-benzimidazole hydrochloride**

To a stirred solution of (E)-3-cyclopentylacrylic acid (0.40 g, 2.85 mmol, Roth, R.; Erlenmeyer, H. Helv. Chim. Acta, 38, 1955, 1276) in dichloromethane (20 ml) at 0 °C under a nitrogen atmosphere was added oxalyl chloride (1.46 g, 11.5 mmol). The mixture was stirred at 0 °C for 40 min and then at room temperature for 100 min. Evaporation of volatiles under reduced pressure gave 3-cyclopentylacryloyl chloride as a colorless liquid, which was used without

purification.

To a stirred solution of *N*-phenyl-*o*-phenylenediamine (0.38 g, 3.0 mmol) in xylenes (35 ml) was added a solution of 3-cyclopentylacryloyl chloride (2.85 mmol) in xylenes (20 ml) during 10 min in a dropwise manner. The resulting mixture was stirred at room temperature for 80 min and then at reflux to remove water using a Dean-Stark apparatus for about 13 h. To the mixture was added *p*-toluenesulfonic acid monohydrate (0.10 g) and the reaction was continued for 10 h. After cooling, volatiles were removed by evaporation and the residue was dissolved into a mixture of ethyl acetate (100 ml) and saturated aqueous sodium bicarbonate solution (100 ml). The organic layer was dried (magnesium sulfate) and concentrated to dryness. Silica-gel column chromatography (silica gel, 100 g; *n*-hexane/ethyl acetate (4/1 to 7/3)) afforded 0.15 g (18%) of (*E*)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole as an amber oil. The oil was dissolved into ethyl ether and hydrogen chloride gas was passed through the stirred solution. Volatiles were removed by evaporation and the residue was triturated with diisopropyl ether. Precipitates were collected by suction, washed with diisopropyl ether and dried under vacuum to give the titled compound as white solids.

MW: 324.86

mp: 136.0-137.0°C (decomposition)

¹H-NMR (DMSO-*d*₆) δ: 7.86-7.60 (6 H, m), 7.57-7.38 (2 H, m), 7.32-7.11 (2 H, m), 6.23 (1H, d, J = 15.8 Hz), 2.78-2.66 (1H, m), 1.82-1.75 (2 H, m), 1.73-1.50 (4 H, m), 1.45-1.29 (2 H, m)

Example 22

2-Phenylethynyl-1-phenyl-1*H*-benzimidazole

The titled compound was prepared from *N*-phenyl-*o*-phenylenediamine and phenylpropynoyl chloride (Bergmann, F.; Haskelberg, L. J. Am. Chem. Soc., 63, 1941, 2243) according to the preparation of (*E*)-1-phenyl-2-styryl-1*H*-benzimidazole (example 1).

MW: 294.36

mp: 118.0-119.0°C

¹H-NMR (CDCl₃) δ: 7.87-7.82 (1 H, m), 7.64-7.49 (5 H, m), 7.43-7.27 (8 H, m)

Example 23

(*Z*)-1-Phenyl-2-styryl-1*H*-benzimidazole

To a solution of 2-phenylethynyl-1-phenyl-1*H*-benzimidazole (0.98 g, 3.0 mmol) in toluene (30 ml) were added quinoline (10 drops) and palladium on calcium carbonate (0.20 g) and the reaction mixture was vigorously stirred for 1 h under a hydrogen atmosphere. Catalyst was removed by filtration and the filtrate was concentrated in vacuo. Purification by column chromatography (silica gel, 250 g; *n*-hexane/ethyl acetate (5/1)) gave 0.53 g (54%) of the titled compound (R_f=0.2) as a colorless oil.

MW: 296.37

mp: OIL

¹H-NMR (CDCl₃) δ: 7.83 (1 H, dd, J = 8.4, 1.8 Hz), 7.48-7.38 (5 H, m), 7.34-7.16 (8 H, m), 6.78 (1 H, d, J = 12.8 Hz), 6.39 (1 H, d, J = 12.8 Hz)

Example 24

(*E*)-1-Phenyl-2-[2-(2-pyridyl)vinyl]-1*H*-benzimidazole

1. *N*-(2-Anilinophenyl)-3-(2-pyridyl)acrylamide

To a stirred solution of (*E*)-3-(2-pyridyl)acrylic acid (0.44 g, 3.0 mmol, Ried, W.; Keller, H. Chem. Ber., 89, 1955, 2578), *N*-phenyl-*o*-phenylenediamine (0.61 g, 3.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.69 g, 3.6 mmol) in dimethylformamide (5 ml) at -20 °C under a nitrogen atmosphere was added triethylamine (0.7 ml). The resulting mixture was stirred at -18 to -8 °C for 40 min and then at room temperature for 8 h. The mixture was diluted with water (50 ml) and extracted with ethyl acetate (50 ml). The organic extract was washed consecutively with water (50 ml) and brine (50 ml), dried (magnesium sulfate) and concentrated to dryness. Column chromatography (silica gel, 85 g; *n*-hexane/ethyl acetate (1/1)) afforded 0.40 g (42%) of *N*-(2-anilinophenyl)-3-(2-pyridyl)acrylamide as

an orange liquid.

¹H-NMR (CDCl₃) δ: 8.63-8.59 (1 H, m), 8.24-8.16 (1 H, m), 8.03 (1 H, br. s), 7.75-7.68 (1 H, m), 7.69 (1 H, d, J = 15.0 Hz), 7.40-7.36 (1 H, m), 7.30-7.12 (6 H, m), 7.08 (1 H, d, J = 15.0 Hz), 6.91-6.85 (1 H, m), 6.82-6.75 (2 H, m), 5.55 (1 H, br. s).

2. (E)-1-Phenyl-2-[2-(2-pyridyl)vinyl]-1H-benzimidazole

A stirred mixture of *N*-(2-anilinophenyl)-3-(2-pyridyl)acrylamide, *p*-toluenesulfonic acid monohydrate (0.48 g, 2.5 mmol) and xylenes (80 ml) was heated to reflux to remove water using a Dean-Stark apparatus for 4 h. After cooling, the mixture was concentrated to dryness and the residue shaken with ethyl acetate (100 ml) and saturated aqueous sodium bicarbonate solution (50 ml). The aqueous layer was separated and extracted with ethyl acetate (2 X 100 ml). The combined organic layers were dried (magnesium sulfate) and concentrated to dryness. The crude product was purified by column chromatography (silica gel, 85 g; *n*-hexane/ethyl acetate (1/2)) to afford 0.29 g of product as reddish solids. Recrystallization from diisopropyl ether/ethyl acetate (5/1) afforded 0.17 g (45%) of the titled compound as white solids.

MW: 297.36

mp: 144.0-145.0°C

¹H-NMR (CDCl₃) δ: 8.58-8.53 (1 H, m), 7.99 (1 H, d, J = 15.6 Hz), 7.88-7.83 (1 H, m), 7.71-7.57 (4H, m), 7.52 (1 H, d, J = 15.6 Hz), 7.49-7.44 (2 H, m), 7.38-7.14 (5 H, m)

Example 25

(E)-1-Phenyl-2-[2-(4-pyridyl)vinyl]-1H-benzimidazole

The titled compound was prepared from *N*-phenyl-*o*-phenylenediamine and (E)-3-(4-pyridyl)acrylic acid according to the preparation of (E)-1-phenyl-2-[2-(2-pyridyl)vinyl]-1H-benzimidazole (example 24).

MW: 297.36

mp: 116.0-117.5 °C

¹H-NMR (CDCl₃) δ: 8.60-8.56 (2 H, m), 7.88-7.83 (1 H, m), 7.87 (1 H, d, J = 16.1 Hz), 7.70-7.56 (3H, m), 7.48-7.42 (2 H, m), 7.39-7.32 (1 H, m), 7.31-7.19 (4 H, m), 7.04 (1 H, d, J = 16.1 Hz)

Example 26

(E)-2-[2-(2-Oxazolyl)vinyl]-1-phenyl-1H-benzimidazole

1. Ethyl (E)-2-(1-phenyl-1H-benzimidazol-2-yl)propenoate

Ethyl (E)-2-(1-phenyl-1H-benzimidazol-2-yl)propenoate was prepared from *N*-phenyl-*o*-phenylenediamine and ethyl 3-chlorocarbonylacrylate (Home, S.; Taylor, N.; Collins, S.; Rodrigo, R. J. Chem. Soc. Perkin Trans. 1, 12, 1991, 3047) according to the preparation of (E)-1-phenyl-2-styryl-1H-benzimidazole (example 1).

¹H-NMR (CDCl₃) δ: 7.88-7.83 (1 H, m), 7.66-7.55 (3 H, m), 7.42 (1 H, d, J = 15.4 Hz), 7.41-7.19 (5 H, m), 7.15 (1 H, d, J = 15.4 Hz), 4.23 (2 H, q, J = 7.0 Hz), 1.30 (3 H, t, J = 7.0 Hz).

2. (E)-2-(1-Phenyl-1H-benzimidazol-2-yl)propenoic acid

To a solution of ethyl (E)-2-(1-phenyl-1H-benzimidazol-2-yl)propenoate (3.74 g, 12.8 mmol) in a mixture of methanol (18 ml) and tetrahydrofuran (18 ml) was added a 4 N aqueous solution of lithium hydroxide (6 ml, 24 mmol) and the reaction mixture was stirred for 3 h at room temperature. To the reaction mixture was added 4 N hydrochloric acid (6ml, 24mmol) at 0 °C. The precipitated solids were collected by the filtration and dried under reduced pressure to afford 2.70 g (80%) of (E)-2-(1-Phenyl-1H-benzimidazol-2-yl)propenoic acid as white solids.

¹H-NMR (DMSO-d₆) δ: 7.89 (1 H, d, J = 7.3 Hz), 7.84-7.62 (5 H, m), 7.48-7.26 (4 H, m), 6.97 (1 H, d, J = 15.4 Hz).

3. 3-(1-Phenyl-1H-benzimidazol-2-yl)acrylamide

To a stirred solution of 3-(1-phenyl-1H-benzimidazol-2-yl)acrylic acid (1.06 g, 4 mmol) in dichloromethane (80 ml) at 0 °C under a nitrogen atmosphere was added oxalyl chloride (3.05 g, 24 mmol) and the resulting suspension was

stirred at 0 °C for 20 min and then at room temperature for 2.5 h. Volatiles were removed by evaporation and the residue was added in portions to a stirred 25% aqueous solution of ammonia (40 ml). After 130 min, solids were collected by suction, washed with water and dried under vacuum at 50 °C to give 1.04 g (98%) of the titled compound as off-white solids.

¹H-NMR (CDCl₃) δ: 7.86-7.91 (1 H, m), 7.66-7.55 (3 H, m), 7.45 (1 H, d, J = 15.0 Hz), 7.43-7.19 (6 H, m), 5.65 (1 H, br. s), 5.55 (1 H, br. s).

4. (E)-2-[2-(2-Oxazolyl)vinyl]-1-phenyl-1H-benzimidazole

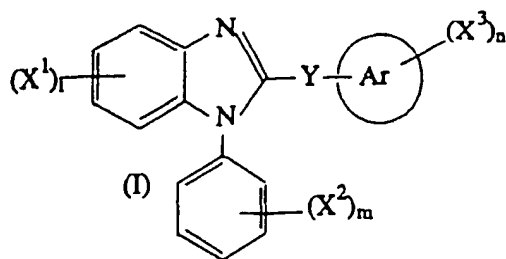
A mixture of 3-(1-phenyl-1H-benzimidazol-2-yl)acrylamide (0.62 g, 2.35 mmol), vinylene carbonate (0.26 g, 3.0 mmol) and polyphosphoric acid (6.2 g) was stirred at 170 °C. After 2 h, ice was added and the mixture was basified with a 10% aqueous solution of potassium hydroxide (100 ml) and extracted with dichloromethane/isopropyl alcohol (9/1, 150 ml + 50 ml). The combined organic layers were washed consecutively with water (2 X 100 ml) and brine (100 ml), dried (magnesium sulfate) and concentrated to dryness. Purification by column chromatography (silica gel 100 g, ethyl acetate) afforded 66 mg of product as pale green solids which were recrystallized from diisopropyl ether to afford 36 mg (5%) of the titled compound as tan solids.

MW: 287.32

mp: 155.5-156.0°C

¹H-NMR (CDCl₃) δ: 7.89-7.84 (1 H, m), 7.73 (1 H, d, J = 16.1 Hz), 7.68-7.54 (4 H, m), 7.47-7.42 (2 H, m), 7.39-7.32 (1 H, m), 7.31-7.25 (1 H, m), 7.27 (1 H, d, J = 16.1 Hz), 7.23-7.18 (2 H, m)

The chemical structures of the compounds prepared in the Examples 1 to 26 are summarized in the following tables.

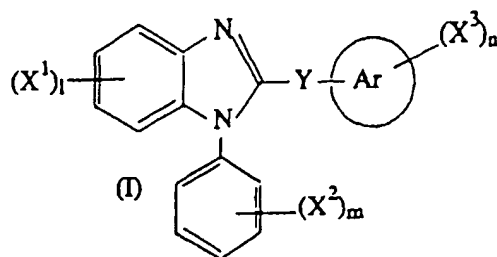
TABLE

Ex. #	Ar	Y	X¹	X²	X³
1*	phenyl	(E) CH=CH	-	-	-
2	phenyl	(E) CH=CH	-	-	4-F
3	phenyl	(E) CH=CH	-	-	3-F
4	phenyl	(E) CH=CH	-	-	2-F
5	phenyl	(E) CH=CH	-	-	4-MeS
6	phenyl	(E) CH=CH	-	-	4-MeS(O)
7	phenyl	(E) CH=CH	-	-	4-MeS(O)₂
8	phenyl	(E) C(CH₃)=CH	-	-	-
9	phenyl	(E) CH=CH	6-Cl	-	-
10	phenyl	(E) CH=CH	5-Cl	-	-
11	phenyl	(E) CH=CH	-	4-F	-
12	phenyl	(E) CH=CH	-	4-F	4-MeS
13	phenyl	(E) CH=CH	-	4-MeS	4-F
14	phenyl	(E) CH=CH	5-NO₂	-	-
15	phenyl	(E) CH=CH	5-NH₂	-	-
16	phenyl	(E) CH=CH	5-Br	-	-
17	phenyl	(E) CH=CH	5-CN	-	-
18	phenyl	(E) CH=CH	5-CONH₂	-	-
19	3-pyridyl	(E) CH=CH	-	-	-
20	cyclohexyl	(E) CH=CH	-	-	-
21	cyclopentyl	(E) CH=CH	-	-	-
22	phenyl	C≡C	-	-	-
23	phenyl	(Z) CH=CH	-	-	-
24	2-pyridyl	(E) CH=CH	-	-	-
25	4-pyridyl	(E) CH=CH	-	-	-
26	oxazolyl	(E) CH=CH	-	-	-

* To be used in a pharmaceutical composition

Claims

1. A compound of the following formula:



and the pharmaceutically acceptable salts thereof wherein

Ar is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl which is connected to Y through a carbon atom, the heteroaryl being selected from pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isooxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl and tetrazolyl;

X¹ is H, halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkyl, (C₁₋₄) alkoxy(C₁₋₄)alkyl, amino, C₁₋₄ alkylamino, di(C₁₋₄)alkylamino, amino C₁₋₄ alkyl, (C₁₋₄)alkylamino(C₁₋₄)alkyl, di(C₁₋₄)alkylamino(C₁₋₄)alkyl, C₁₋₄ alkanoylamino, di(C₁₋₄)alkanoylamino, (C₁₋₄)alkyl(C₁₋₄)alkanoylamino, C₁₋₄ alkylsulfonylamino, C₁₋₄ alkanoyl, carboxyl, (C₁₋₄)alkoxycarbonyl, aminocarbonyl, (C₁₋₄)alkylaminocarbonyl, di(C₁₋₄)alkylaminocarbonyl, cyano, nitro, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylaminosulfonyl or di(C₁₋₄)alkylaminosulfonyl;

X² and X³ are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkanoyl, carboxyl, (C₁₋₄)alkoxycarbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl, di(C₁₋₄)alkylaminocarbonyl, cyano, nitro, amino, C₁₋₄ alkylamino, di(C₁₋₄)alkylamino or C₁₋₄ alkylsulfonylamino;

Y is -CR¹=CR² or -C≡C-, wherein R¹ and R² are independently H, methyl, ethyl or halo;

1 is 0, 1, 2, 3 or 4; and

m and n are independently 0, 1, 2 or 3,

with the proviso that when Ar is phenyl; and 1, m and n are 0, Y is not CH=CH-; and when Ar is phenyl; 1 and m are 0; n is 1; and Y is -CH=CH-, X³ is not C₁₋₄ alkoxy attached to the 2-position of Ar, nor amino, C₁₋₄ alkylamino or di(C₁₋₄)alkylamino attached at the 4-position of Ar.

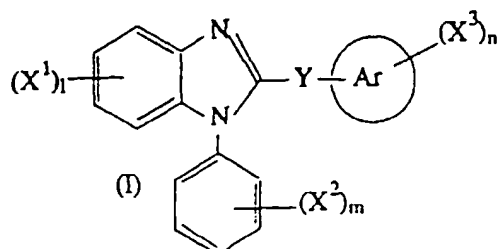
2. A compound according to claim 1, wherein Ar is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl selected from pyridyl, pyrrolyl and oxazolyl; X² and X³ are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; X¹ is H, halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkyl, amino, C₁₋₄ alkylamino, cyano or nitro; 1 is 0 or 1; and m and n are independently 0 or 1.
3. A compound according to claim 2, wherein Ar is phenyl or C₃₋₈ cycloalkyl; X² and X³ are independently, halo, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; X¹ is H, halo, amino, cyano or nitro, which is attached to 5-or 6-ring position of the benzimidazole ring system; and Y is -CR¹=CR²-, wherein R¹ and R² are independently H or methyl.
4. A compound according to claim 3, wherein Ar is phenyl, cyclopentyl or cyclohexyl; X² and X³ are independently, fluoro, methylthio, methylsulfinyl or methylsulfonyl; X¹ is H, fluoro, chloro, bromo, amino, cyano or nitro, which is attached to 5-ring position of the benzimidazole ring system; and Y is -CH=CH-.
5. A compound according to claim 1 selected from

(E)-2-(4-fluorostyryl)-1-phenyl-1H-benzimidazole;
 (E)-2-(2-fluorostyryl)-1-phenyl-1H-benzimidazole hydrochloride;
 (E)-5-nitro-1-phenyl-2-styryl-1H-benzimidazole
 (E)-5-amino-1-phenyl-2-styryl-1H-benzimidazole dihydrochloride;
 (E)-5-bromo-1-phenyl-2-styryl-1H-benzimidazole;
 (E)-5-cyano-1-phenyl-2-styryl-1H-benzimidazole;
 (E)-2-(2-cyclohexylvinyl)-1-phenyl-1H-benzimidazole;
 (E)-2-(2-cyclopentylvinyl)-1-phenyl-1H-benzimidazole hydrochloride; and
 (E)-1-phenyl-2-[2-(2-pyridyl)vinyl]-1H-benzimidazole.

6. A compound according to claim 5 selected from

(*E*)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole;
 (*E*)-5-cyano-1-phenyl-2-styryl-1*H*-benzimidazole; and
 (*E*)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole hydrochloride.

7. A pharmaceutical composition which comprises a compound of the following formula I);



and the pharmaceutically acceptable salts thereof wherein

Ar is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl which is connected to **Y** through a carbon atom, the heteroaryl being selected from pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isooxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl and tetrazolyl;

X¹ is H, halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkyl, (C₁₋₄) alkoxy(C₁₋₄) alkyl, amino, C₁₋₄ alkylamino, di(C₁₋₄) alkylamino, amino C₁₋₄ alkyl, (C₁₋₄) alkylamino(C₁₋₄) alkyl, di(C₁₋₄) alkylamino(C₁₋₄) alkyl, C₁₋₄ alkanoylamino, di(C₁₋₄) alkanoylamino, (C₁₋₄) alkyl(C₁₋₄) alkanoyl amino, C₁₋₄ alkylsulfonylamino, C₁₋₄ alkanoyl, carboxyl, (C₁₋₄) alkoxycarbonyl, aminocarbonyl, (C₁₋₄) alkylaminocarbonyl, di(C₁₋₄) alkylaminocarbonyl, cyano, nitro, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, aminosulfonyl, C₁₋₄ alkylaminosulfonyl or di(C₁₋₄) alkylaminosulfonyl;

X² and **X³** are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, mercapto, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkanoyl, carboxyl, (C₁₋₄) alkoxycarbonyl, aminocarbonyl, C₁₋₄ alkylaminocarbonyl, di(C₁₋₄) alkylaminocarbonyl, cyano, nitro, amino, C₁₋₄ alkylamino, di(C₁₋₄) alkylamino or C₁₋₄ alkylsulfonylamino;

Y is -CR¹=CR²- or -C≡C-, wherein **R¹** and **R²** are independently H, methyl, ethyl or halo;

1 is 0, 1, 2, 3 or 4; and

m and n are independently 0, 1, 2 or 3,

and a pharmaceutically inert carrier or diluent.

8. A pharmaceutical composition according to claim 7, wherein **Ar** is phenyl, C₃₋₈ cycloalkyl, C₄₋₈ cycloalkenyl or heteroaryl selected from pyridyl, pyrrolyl and oxazolyl; **X²** and **X³** are independently C₁₋₄ alkyl, halo, halo-substituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; **X¹** is H, halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halo-substituted C₁₋₄ alkyl, hydroxy-substituted C₁₋₄ alkyl, amino, C₁₋₄ alkylamino, cyano or nitro; 1 is 0 or 1; and m and n are independently 0 or 1.

9. A pharmaceutical composition according to claim 8, wherein **Ar** is phenyl or C₃₋₈ cycloalkyl; **X²** and **X³** are independently, halo, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl or C₁₋₄ alkylsulfonyl; **X¹** is H, halo, amino, cyano or nitro, which is attached to 5- or 6-ring position of the benzimidazole ring system; and **Y** is -CR¹=CR²-, wherein **R¹** and **R²** are independently H or methyl.

10. A pharmaceutical composition according to claim 9, wherein **Ar** is phenyl, cyclopentyl or cyclohexyl; **X²** and **X³** are independently, fluoro, methylthio, methylsulfinyl or methylsulfonyl; **X¹** is H, fluoro, chloro, bromo, amino, cyano or nitro, which is attached to 5-ring position of the benzimidazole ring system; and **Y** is -CH=CH-.

11. A pharmaceutical composition according to claim 7, wherein the compound is selected from

(*E*)-1-phenyl-2-styryl-1*H*-benzimidazole;

(E)-2-(4-fluorostyryl)-1-phenyl-1*H*-benzimidazole;
 (E)-2-(2-fluorostyryl)-1-phenyl-1*H*-benzimidazole hydrochloride;
 (E)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-amino-1-phenyl-2-styryl-1*H*-benzimidazole dihydrochloride;
 (E)-5-bromo-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-cyano-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-2-(2-cyclohexylvinyl)-1-phenyl-1*H*-benzimidazole;
 (E)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole hydrochloride; and
 (E)-1-phenyl-2-[2-(2-pyridyl)vinyl]-1*H*-benzimidazole.

12. A pharmaceutical composition according to claim 11, wherein the compound is selected from

(E)-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-nitro-1-phenyl-2-styryl-1*H*-benzimidazole;
 (E)-5-cyano-1-phenyl-2-styryl-1*H*-benzimidazole; and
 (E)-2-(2-cyclopentylvinyl)-1-phenyl-1*H*-benzimidazole hydrochloride.

13. A compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof as claimed in any one of claims 1 to 6 and 7 to 12, respectively, for use as a medicament.

14. The use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition *thereof*, as claimed in any one of claims 1 to 6 and 7 to 12, respectively, for the manufacture of a medicament for treating a medical condition in which prostaglandins are implicated as pathogens in a mammalian subject.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 30 9761

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	CHEMICAL ABSTRACTS, vol. 82, no. 9, 3 March 1975 Columbus, Ohio, US; abstract no. 57696d, page 574; XP002059542	1,7,13, 14	C07D235/08 C07D235/10 C07D235/12 C07D235/14 C07D235/16 C07D401/06 C07D413/06 A61K31/415 A61K31/42 A61K31/44
D	& JP 49 081 369 A (TOBISHI PHARMACEUTICAL CO., LTD.) 6 August 1974 ---		
Y	EP 0 419 210 A (PFIZER INC.) * claims 1,7-9 *	1,7,13, 14	
D,X	PATENT ABSTRACTS OF JAPAN vol. 8, no. 183 (P-296), 23 August 1984 & JP 59 075257 A (RICOH KK), 27 April 1984, * formula I * * abstract *	1	
A	EP 0 608 548 A (KONICA CORP.) * pages 9-11, formulae I-23, I-30, I-36 * D & JP 06 194 780 A ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D
A	US 3 586 670 A (P. BRENNEISEN ET AL.) * table VI, compounds no. 3, 4 and 28 * * claims 1,2,5 *	1	
A	DE 19 62 353 A (FARBENFABRIKEN BAYER AG) * page 20; example 5 * -----	1	
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 19 March 1998	Examiner Hass, C
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 (03.82) (P/4/01)